Short-term synaptic plasticity and the 'active calcium' hypothesis at a central synapse

Philippe Isope
Institut des Neurosciences Cellulaires et Intégratives, CNRS, Université de Strasbourg, 5, rue Blaise Pascal, 67084, Strasbourg, France
Email: philippe.isope@inci-cnrs.unistra.fr

Short-term synaptic plasticity reflects the recent history of synaptic inputs and directly influences information processing in a neural network. Different forms of facilitation and depression of transmission following doublet or train stimulations, lasting tens to hundreds of milliseconds, have been demonstrated over the last four decades. However, there is still no consensus on the precise aetiology of the underlying mechanisms. In a recent issue of The Journal of Physiology, the article by Bornschein et al. (2013), nicely combines state of the art electrophysiological and two-photon imaging techniques to tackle the origin of a very short-term facilitation (5–10 ms time course) observed at the cerebellar Purkinje cell recurrent collateral –Purkinje cell synapse (Orduz & Llano, 2007).

The basic concept in paired-pulse dependent short-term plasticity is that calcium-dependent vesicular release triggered by one action potential (AP) conditions the response of the release machinery to an AP occurring shortly after (Zucker & Regehr, 2002). Several non-exclusive mechanisms yielding a short-term increase in the probability of release of synaptic vesicles have been proposed; initially, it was suggested (Mallart & Martin, 1967; Katz & Miledi, 1968) that the calcium ions remaining bound to the inner part of the plasma membrane could lead to facilitation as an 'active compound'. Three decades later, synaptotagmins (Syts) have been identified as the main Ca 2+ sensors in AP-evoked vesicular release (Chapman, 2008). These low affinity calcium sensors require micromolar calcium to trigger release, thus implying that calcium channels and vesicles are in very close proximity. The residual calcium after a first AP represents a negligible increase in calcium concentration (a few tens of nanomolar) and given the low affinity of Syts for Ca 2+, residual Ca 2+ can hardly explain the enhanced synaptic release. As calcium is released from Syt very rapidly (a few milli-seconds), the several hundred millisecond duration of most paired-pulse facilitation observed at CNS synapses cannot be explained by the remaining calcium bound to Syt. Several mechanisms have been proposed.

(1) It has been postulated that short-term facilitation could be due to a specific high affinity calcium sensor that binds calcium for hundreds of milli-seconds and increase release probability. The fact that manipulation of mobile intra-cellular calcium buffers (genetic ablation of parvalbumin or loading with EGTA,
an exogenous buffer) can affect the time course of the facilitation without altering phasic release at some synapses argues in favour of this putative second sensor.

(2) Calcium-binding proteins with a fast binding rate such as calbindin, which can intercept calcium ions between the mouth of the channel and the Syt, might affect initial probability of release. Then if the calcium influx from a first AP saturates this buffer, a second calcium influx could increase the level of calcium and the probability of release leading to facilitation.

(3) Direct regulation of calcium channels via calcium sensor proteins has also been demonstrated at the Calyx of Held.

(4) Finally, high frequency stimulation has recently been shown to recruit reluctant release sites and this might also explain facilitation (Valera et al. 2012).

At the Purkinje cell – Purkinje cell synapse, calcium entry through calcium channels sums linearly between APs (Orduz & Llano, 2007), ruling out facilitation of calcium influx. Bornschein et al. have used two-photon calcium imaging combined with paired recordings to control both the pre- and postsynaptic compartments and change internal calcium buffering by adding exogenous buffers (such as EGTA) via the patch pipette. They also used transgenic mice in which calbindin or parvalbumin were deleted to study the influence of calcium sensor proteins. The most striking result was that neither the removal of endogenous buffers nor the addition of exogenous buffer affected the short-term facilitation. In calbindin −/−mice, the probability of release and the level of calcium in the presynaptic terminal were increased as expected for a fast calcium buffer, whereas no effect was observed in parvalbumin −/− animals. These results strongly suggest that residual calcium or buffer saturation cannot explain the observed facilitation. These findings also indicate that synaptic vesicles must be very close to calcium channels and that diffusion of calcium is restricted. Indeed, using experimentally constrained modelling, the coupling distance was estimated to be <100 nm, and the diffusion of calcium limited. Using several models for synaptic release, they finally demonstrated that the residual occupancy of Syt (10–20% after 5 ms) after an AP can fully explain the observed facilitation, hence revisiting the 'active calcium' hypothesis from Katz and Miledi (1968).

What is the physiological relevance of this facilitation observed only if Purkinje cells fire at 200 Hz? Although this frequency is hardly observed during spontaneous discharge, parallel fibre or climbing fibre inputs can elicit bursts of APs that can reach several hundred Hertz. High frequency stimulation would then favour Purkinje cell inhibition by collaterals of their connected neighbours. Since Purkinje cell collaterals follow the parasagittal modular organization of the cerebellar cortex, this recurrent inhibition might contribute to the synchronization of functionally related Purkinje cells (De Solages et al. 2008), yielding a tight control of the targeted cerebellar nuclear cells. By contrast, the Purkinje cell to nuclear cell connection exhibits a strong paired-pulse depression, leading to a near absence of transmission after the first stimulation at 200 Hz (Pedroarena & Schwarz, 2003). Further work is required to address this issue, and it would be particularly interesting to understand how the underlying release machinery is precisely organized at both synaptic sites to create this dichotomy and what are the consequences on the read-out by nuclear cells, the output of the cerebellum.

References

Bornschein G, Arendt O, Hallermann S, Brachtendorf S, Eilers J & Hartmut Schmidt (2013). JPhysiol591, 3355–3370.
Chapman ER (2008). Annu Rev Biochem 77, 615–641.
De Solages C, Szapiro G, Brunel N, Hakim V, Isope P, Buisseret P, Rousseau C, Barbour B & Léna C (2008). Neuron 58, 775–788.
Katz B & Miledi R (1968). JPhysiol195, 481–492.
Mallart A & Martin AR (1967). JPhysiol193, 679–694.
Orduz D & Llano I (2007). Proc Natl Acad Sci USA104, 17831–17836.
Pedroarena CM & Schwarz C (2003). JNeurophysiol89, 704–715.
Valera AM, Doussau F, Poulain B, Barbour B & Isope P. (2012). JNeurosci32, 3267–3280.
Zucker RS & Regehr WG (2002). Annu Rev Physiol 64, 355–405.